

# Attention deficit hyperactivity disorder (ADHD): from a childhood neuropsychiatric disorder to an adult condition

Rita Vadalà, MD<sup>a</sup>, Elisabetta Giugni, MD<sup>b</sup>, Anna Pichiecchio MD<sup>c</sup>, Umberto Balottin, MD<sup>c</sup>, Stefano Bastianello, MD, PhD<sup>c</sup>

<sup>a</sup> IRCCS S. Lucia Foundation, Rome, Italy

<sup>b</sup> European Biomedical Foundation, Onlus, Rome, Italy

<sup>c</sup> IRCCS C. Mondino National Institute of Neurology Foundation, University of Pavia, Italy

Attention deficit hyperactivity disorder (ADHD) is one of the most common childhood neuropsychiatric disorders and it often persists into adulthood; it is a neurobiological syndrome with an estimated prevalence among children and adolescents of 5%. The psychopathology of this disorder is marked by developmentally inappropriate and pervasive expressions of inattention, overactivity and impulsiveness. ADHD is also associated with functional impairments across multiple academic and social domains and is commonly accompanied by a range of externalising and internalising disorders. The most recent definition of ADHD in the fourth edition of the *Diagnostic and Statistical Manual of Mental Disorders (DSM-IV)* distinguishes between diagnostic subtypes characterised by maladaptive levels of both inattention and hyperactivity-impulsivity (combined type), maladaptive levels of inattention only (predominantly inattentive type), and maladaptive levels of hyperactivity-impulsivity alone (predominantly hyperactive-impulsive type). Behavioural genetic studies indicate that ADHD is significantly familial, and that this familiarity is primarily due to genetic influences. In addition, non-shared environmental factors specific to the individual account for significant variance in ADHD. Numerous studies have attempted to identify the specific environmental or genetic factors that increase the likelihood of a child developing ADHD; these studies clearly suggest that multiple genes are involved in the aetiology of ADHD, and that few, if any, of these genes are necessary or sufficient to cause ADHD. The aetiology of ADHD is multifactorial. A genetic cause linked to dopamine deficit is frequent and primary, but various environmental factors, including viral infection, maternal smoking during pregnancy, prematurity, cerebral hypoxic ischaemia, alcohol exposure, and nutritional and endocrine disorders may contribute as secondary causes. The aetiology is probably a combination of genetic and acquired factors in most cases.

The neuroanatomical basis of ADHD is postulated to involve brain circuitry responsible for attention and executive function.

In recent years, a change in perspective in aetiological models of ADHD has occurred in concordance with emerging concepts in other neuropsychiatric disorders such as schizophrenia and autism. These models shift the focus of the assumed pathology from regional brain abnormalities to dysfunction in distributed network organisation.

Advanced magnetic resonance imaging (MRI) techniques involving diffusion tensor imaging (DTI), functional magnetic resonance imaging (fMRI), magnetic resonance spectroscopy (MRS) and morphometry have greatly increased understanding of the neurobiology of ADHD.

fMRI studies have identified multiple nodes of dysfunction in frontostriatal and mesocorticolimbic networks in ADHD. However, relatively few studies have examined how structural and functional connectivity between nodes in these networks might relate to the behavioural symptoms of ADHD. Moreover, it is unknown whether abnormalities in connectivity are a primary cause of symptoms or arise secondary to common aetiological mechanisms.

DTI studies indicate that ADHD is associated with significant irregularities in white matter microstructure, especially in frontostriatal and certain corticocortical tracts.

Resting-state fMRI studies implicate altered connectivity within a default mode network of structures active during introspective, task-free processes and disrupted interactions between this network and frontostriatal attentional systems. Deficits in functional connectivity within frontostriatal and mesocorticolimbic networks might give rise, in part, to ADHD symptoms.

Other studies have demonstrated, as a potential concurrent cause, altered modulation of synaptic potentiation and pruning by dopamine during development.

Collectively, these studies suggest that the core symptoms of ADHD might derive from dysregulated modulation of cortical plasticity in the developing brain, resulting in altered patterns of corticocortical connectivity that might persist into adulthood.

Given the burden of ADHD on society, families and individuals, understanding its underlying causes and developing new and more effective treatments to target them are important objectives for neuroscience research. Indeed, in at least 15% of ADHD children the disorder persists into adulthood, while an additional 50% have a partial diagnosis in adulthood with persistence of some symptoms leading to continued impairments. Furthermore, most of these 'partial

remission' cases are expected, in the future diagnostic criteria (DSM-V) for ADHD, to be re-classified as meeting the full criteria for ADHD in adulthood.

Symptoms of persistent ADHD include inattention, forgetfulness, poor concentration, distractibility, lack of conscientiousness, disorganisation and emotional dysregulation including mood instability and irritability. Hyperactive symptoms are often attenuated as compared to the childhood condition, yet increased motor activity and fidgetiness, impatience, risk taking behaviour and sensation seeking are commonly seen and are highly impairing in some cases.

In addition, ADHD in adults is characterised by high comorbidity rates of severe depression, anxiety disorders and alcohol/drug abuse and dependency, as well as long-term problems with low self-esteem and the development of personality disorders.

Persistence into adulthood profoundly impairs functioning in multiple areas and significantly contributes to a variety of adverse health, social and economic outcomes.

Remission of ADHD in a proportion of patients suggests that it could be influenced if the predictors and mechanisms of remission were known; however, only a small number of studies have looked into potential predictors of persistence and remission of ADHD.

The genetic, cognitive and neural mechanisms that underlie persistence versus remission of ADHD are largely unknown. Some authors have proposed a neurodevelopmental model of ADHD and hypothesised that ADHD is due to an early-onset dysfunction of subcortical brain areas that persists throughout life, and that the prefrontal cortex, which typically develops throughout childhood and adolescence, mediates top-down executive function processes that compensate for the subcortical dysfunctions. The literature on the prognostic value of genetic factors, like the ADHD risk factor in the dopamine D4 receptor (*DRD4*) gene, is contradictory. Research into another candidate gene, the dopamine transporter (*DAT1*) gene, suggests that the allele associated with persistence of ADHD in adults is different from that reported to be associated with childhood ADHD. Several candidate genes for ADHD are involved in synaptogenesis and neuronal alignment and adhesion. It has been suggested that altered synaptic reinforcement and extinction processes define an endophenotype in ADHD that can be related dimensionally to inattention, hyperactivity, and impulsivity.

Finding a cognitive or biological marker of persistent ADHD would provide a means of identifying children with ADHD who are at risk of a persistent course into adulthood and poor clinical and psychosocial outcomes.

Technical advances in genetic analysis, proteomics, systems analysis, and the availability of established cell-based and animal-based model systems for the evaluation of genes and their interaction with the environment, are finally bringing the identification of biological markers for persistence of ADHD within close reach.

It will be crucial to combine biological marker data with those derived from neuroimaging analysis and from neuropsychology and neuropsychopharmacology studies, in order to define a test for ADHD persistence with high sensitivity and specificity.

Such markers would provide a basis for developing targeted treatment approaches for the group at risk of persistence. In addition, resilience factors that increase the chance of remission could also be identified in this way, allowing the development of strategies for better coping with the disorder. Targeting processes that naturally lead to remission in a proportion of cases may lead to the development of new treatments to prevent progression of the disorder in cases in which ADHD would usually persist.

A promising future direction for recent neuroimaging and neuromolecular studies could be to investigate parallels between clinical features (behavioural and cognitive) and neurobiological findings in ADHD and neurodegenerative diseases during early onset. The hypothesis of a link between ADHD and neurodegenerative diseases, like amyotrophic lateral sclerosis or Parkinson's disease, provides a possible example of how research into neurodevelopmental diseases might influence understanding of neurodegenerative diseases.

## Essential bibliography

Amico F, Stauber J, Koutsouleris N, Frodl T. Anterior cingulate cortex gray matter abnormalities in adults with attention deficit hyperactivity disorder: A voxel-based morphometry study. *Psychiatry Res* 2011;191:31-35

Bilenberg N, Hougaard D, Norgaard-Pedersen B, Nordenbæk CM, Olsen J. Twin study on transplacental-acquired antibodies and attention deficit/hyperactivity disorder – a pilot study. *J Neuroimmunol* 2011;236:72-75

Brown AB, Biederman J, Valera E et al. Relationship of DAT1 and adult ADHD to task-positive and task-negative working memory networks. *Psychiatry Res* 2011;193:7-16

Broyd SJ, Demanuele C, Debener S et al. Default-mode brain dysfunction in mental disorders: a systematic review. *Neurosci Biobehav Rev* 2009;33:279-296

Bush G. Cingulate, frontal, and parietal cortical dysfunction in attention-deficit/hyperactivity disorder. *Biol Psychiatry* 2011;69:1160-1167

Cao X, Cao Q, Long X et al. Abnormal resting-state functional connectivity patterns of the putamen in medication-naïve children with attention deficit hyperactivity disorder. *Brain Res* 2009;1303:195-206

Durston S, Fossella JA, Casey BJ et al. Differential effects of DRD4 and DAT1 genotype on fronto-striatal gray matter volumes in a sample of subjects with attention deficit hyperactivity disorder, their unaffected siblings, and controls. *Mol Psychiatry* 2005;10:678-685

- Giugni E, Vadalà R, De Vincentiis C, Colica C, Bastianello S. The brain's default mode network: a mind "sentinel" role? *Funct Neurol* 2010;25:189-190
- Kobel M, Bechtel N, Specht K et al. Structural and functional imaging approaches in attention deficit/hyperactivity disorder: Does the temporal lobe play a key role? *Psychiatry Res* 2010;183:230-236
- Konrad K, Eickhoff B. Is the ADHD brain wired differently? A review on structural and functional connectivity in attention deficit hyperactivity disorder. *Hum Brain Mapp* 2010;31:904-916
- Kooij SJ, Bejerot S, Blackwell A et al. European consensus statement on diagnosis and treatment of adult ADHD: The European Network Adult ADHD. *BMC Psychiatry* 2010;10:67
- Liddle EB, Hollis C, Batty MJ et al. Task-related default mode network modulation and inhibitory control in ADHD: effects of motivation and methylphenidate. *J Child Psychol Psychiatry* 2011;52:761-771
- Lule D, Ludolph AC, Ludolph AG. Neurodevelopmental and neurodegenerative diseases – is there a pathophysiological link? Attention-deficit/hyperactivity disorder and amyotrophic lateral sclerosis as examples. *Med Hypotheses* 2008;70:1133-1138
- Millichap JG. Etiologic classification of attention-deficit/hyperactivity disorder. *Pediatrics* 2008;121:e358-65
- Pastura G, Mattos P, Gasparetto EL, Araújo AP. Advanced techniques in magnetic resonance imaging of the brain in children with ADHD. *Arq Neuropsiquiatr* 2011;69:242-252
- Schneider M, Retz W, Coogan A, Thome J, Rösler M. Anatomical and functional brain imaging in adult attention-deficit/hyperactivity disorder (ADHD) – a neurological view. *Eur Arch Psychiatry Clin Neurosci* 2006;256 (Suppl 1):i32-41
- Vaney N, Anjana Y, Khaliq F. No auditory conduction abnormality in children with attention deficit hyperactivity disorder. *Funct Neurol* 2011;26:159-163
- Yang H, Wu QZ, Guo LT et al. Abnormal spontaneous brain activity in medication-naïve ADHD children: a resting state fMRI study. *Neurosci Lett* 2011;502:89-93

